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Kuntscher's Medullary Nailing: In 1940, Kuntscher presented his new method which he recommended for the treatment of fractures of the shafts of all long bones. His method, which is employed after exact reduction of the fragments, consists of the insertion into the marrow cavity of the so-called medullary nail, a long stainless-steel pin, through a small incision at a point away from the fracture site (see News Letter of 4 June 1948). This medullary nail unites the fragments so firmly that, as a rule, the fractured limb can be lifted at once and can be moved actively without additional external support, as with the nailed fracture of the neck of the femur. After bony union, the medullary nail can easily be removed by a simple operation. Closed medullary nailing has 2 great advantages over former types of osteosynthesis, namely, (1) almost complete avoidance of infection, and (2) complete stability, so that, as a rule, no other supports have to be used.

In fractures of the femur, the fragments can slide along the nail and be pressed together. The medullary nail eliminates all detrimental factors of traction and sheering, and only the favorable factor of pressure exists. The callus formation is thereby enhanced, whereas it is often hindered by the use of plates, as the fragments are held apart. Furthermore, with closed medullary nailing, the hematoma and fracture detritus so important for the regeneration of bone are retained, and the periosteum and adjoining tissues are not further traumatized. Therefore, in properly selected fractures of the shaft of the femur, closed medullary nailing is far superior to all known forms of treatment. This method has also proved worth while in the treatment of localized osteitis fibrosa cystica of the femur and the humerus.

The authors, Professor Doctor Lorenz Bohler and Doctor Jorg Bohler of Vienna, Austria, have used medullary nailing since 1940 in about 700 cases. Some time ago, feeling that the results were unsatisfactory in fractures other than those in the femur, the authors reviewed all of their cases. The review indicated that, in bones other than the femur, the results with other methods were better than with medullary nailing. Therefore, they no longer use it for fractures of the tibia or of the forearm and only occasionally in transverse fractures of the humerus.

The theoretical objections raised against medullary nailing have been refuted by practical experience. In adults, the amount of destruction of the bone marrow by the medullary nail is of little significance. Its presence will not cause significant local reaction if a completely inert stainless steel is used; lytic effects are noted only with stainless steel which is not completely inert. The medullary nail hinders callus formation, as does every foreign body, and is not, as Kuntscher thought, conducive to callus formation. An increased formation of callus appears only if the medullary nail does not fix the fragments sufficiently or if an oxidizing metal is used; by the mechanical or electrochemical activity an irritation callus arises, and for a long time the limb cannot be trusted to bear weight.

The insertion of the medullary nail does not cause a clinically evident fat embolism, because by its construction the nail permits the marrow to flow through it, and, therefore, does not act like a piston. Infections are infrequent with medullary nailing. In their own cases the authors have not seen any serious progressive infection as a result of closed medullary nailing. Although the

danger of medullary nailing seems to be small, the authors, in examining about 700 patients in different hospitals, have seen a great many complications due to faulty indications, improper technic, improper instruments, or faulty material. The most serious, and even fatal, incidents occurred because the operation was performed while the patient was in shock.

The most suitable fractures are transverse and short oblique fractures at the middle third of the femur; they should be at least seven centimeters from the tip of the trochanter or from the knee joint. The patient must be in good general condition. The skin must be intact and show no inflammation or burns. Absolutely no shock should be present. This danger is especially great if the nail used is too wide, because too great a force is necessary to drive it in.

The proper instruments must be available, including nails of the proper length and width and sufficient instruments for a bone operation. A special reduction apparatus is necessary for closed nailing. The authors use either their screw-traction apparatus or Wittmoser's reduction apparatus as shown below.

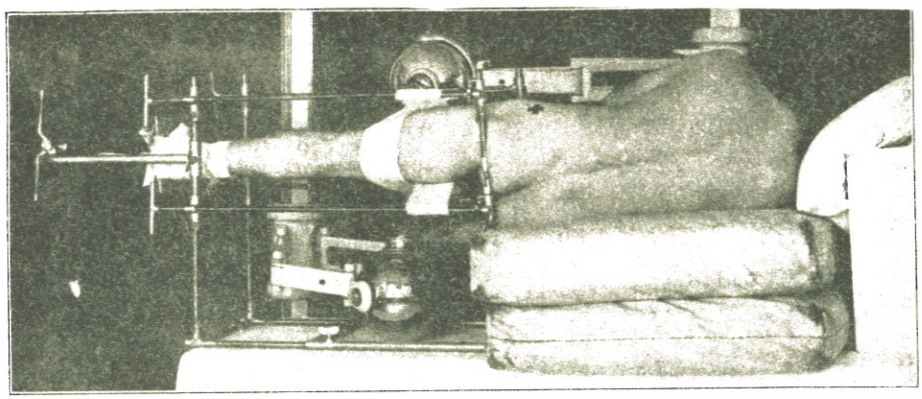

FIG. 1

The femur is fixed for medullary nailing in the Böhler screw-traction apparatus. The patient lies on the well side, bent slightly forward so that the greater trochanter is better exposed. The uninvolved extremity is acutely flexed at the hip. The point of insertion of the medullary nail is marked with a cross. The fragments are reduced and fixed firmly in correct position by means of rotating double bars and canvas slings. Two x-ray tubes are placed in position for fluoroscopy and roentgenography. (Reproduced, by permission of The Williams and Wilkins Company, from *Medullary Nailing of Küntscher*, by Lorenz Böhler.)

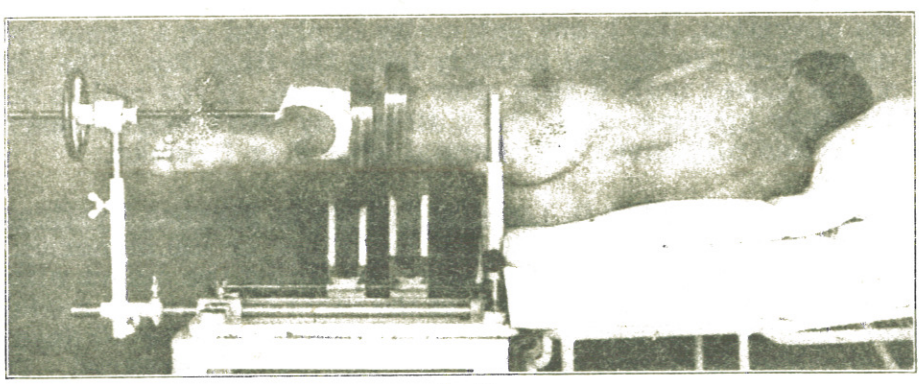

FIG. 2

Fracture of the femur, with patient placed in Wittmoser's reduction apparatus. In fractures close to the knee joint, the knee is flexed to a right angle.

Two portable x-ray machines are needed to afford biplane roentgenographic control without changing the position of the machine.

The operation is performed with repeated roentgenographic checks, so that care must be taken to prevent x-ray burns. An apparatus which reduces the fragments and maintains position mechanically must be used.

Closed Medullary Nailing of the Femur. Closed fractures are best nailed within the first hours of injury. If shock is present, it is well to wait from 8 to 10 days, until the acute reaction has subsided. In the meantime, skeletal traction is applied. After the width and the length of the bone have been determined by means of good roentgenograms and after proper medullary nails have been selected, spinal anesthesia is given, and the patient is placed on a reduction apparatus. With fractures of the lower third of the femur the knee should not be extended, but semiflexed. One x-ray machine is placed at the ventral aspect and a second one at the medial side of the thigh. By means of longitudinal traction, the shortening will be overcome; and by means of canvas slings or wooden rings, attached to rotating bars, the lateral displacement is corrected. If fluoroscopic control shows good reduction from each side, roentgenograms are taken. If they show good alignment of the fragments, the area of the hip is prepared in a sterile manner.

An incision of about from 2 to 3 centimeters in length is made, 5 centimeters above the tip of the trochanter. An awl is inserted to the medial side of the greater trochanter into the marrow cavity. The nail guide is then inserted by means of a handle through this hole, its course being checked by fluoroscopy. As the guide advances toward the knee joint, additional roentgenograms are taken. When they reveal a satisfactory position, the medullary nail is driven over the nail guide with a hammer, again under fluoroscopic control. As the medullary nail approaches the skin, the nail guide is withdrawn and the nail is hammered farther in with a nail-driver, until it extends only two centimeters from the tip of the trochanter and one centimeter from the knee joint. The wound is then closed and again roentgenograms are taken. Should diastasis exist at the fracture site, it is overcome by a strong thrust with the flat of the hand against the knee joint. Reduction may be very difficult and should never be tried without a reduction apparatus. The insertion of the nail guide may also be troublesome, but usually no difficulties arise in driving in a nail of the proper width.

After the operation, the lower extremity is placed on a Braun frame, and the toes and ankle joint are moved actively from the first day. The hip and knee joint should not be moved until 8 days after operation. If the nail is in good position and no other injuries exist, the patient may start weight-bearing after from 8 to 10 days and may leave the hospital after 2 or 3 weeks.

Closed Medullary Nailing in Localized Osteitis Fibrosa Cystica. The cyst is located usually in the upper third of the femur or the humerus. It can be healed by opening and curettage or, better, by filling the defect with bone grafts or bone chips. In one case of cyst of the right humerus, a medullary nail was driven into the cyst and the arm was immobilized for 10 days. Soon afterward the shoulder joint was free and the pain had disappeared. One and one-half years later the nail was withdrawn. The apposition of bone inside the

cyst had taken place without incident.

Unlike curettage and bone-grafting of the area containing the cyst, medullary nailing is a simple procedure and not dangerous. No further fixation is necessary, because the medullary nail gives sufficient support. The authors have operated upon three solitary cysts of the femur by medullary nailing with the same good results. Medullary nailing can also be used in spontaneous fractures occurring at the site of metastases of malignant tumors, which are found mostly in the upper third of the femur. The patients can walk on the extremity with the nail, although the fracture fragments will not reunite.

Open Medullary Nailing of the Femur in Compound Fractures. The authors never use this form of treatment in infected and draining fractures. They use it in all recent compound fractures of the shaft of the femur without joint involvement, and in those patients whose general condition permits. Open medullary nailing is much easier to perform than closed. After exact debridement of the wound, with the patient under local anesthesia, the nail guide is inserted into the central fragment from the fracture site and is advanced through the tip of the trochanter to the skin. A skin incision, 2 or 3 centimeters in length, is made at the point where the guide appears under the skin; and a short medullary nail is driven from above, over the nail guide, one centimeter into the trochanter. The nail guide is pulled out and a new one is inserted from above, through the medullary nail, into the central fragment, until it appears at the fracture site. Then both fragments are approximated and held by means of bone forceps, and the nail guide is inserted into the distal fragment until it reaches the region of the knee joint. If the position of the fragments and of the nail guide is satisfactory, as ascertained by two check roentgenograms, a medullary nail of the proper length and width is driven in and the fragments are impacted by thrusts on the knee with the flat of the hand. Rotation is controlled by means of a longitudinal wire loop. In oblique and spiral fractures, an encircling wire is applied. After insertion of a rubber drain, the skin is closed. The leg is placed on a Braun frame, as is done after closed medullary nailing. The drain is removed after 24 hours. The toes and ankle joint are moved, beginning on the first day. Motion of the knee joint is started 3 weeks later.. If the wound heals without incident, the patient may get up during the fourth week.

To date the authors have nailed about 30 fresh open fractures of the femur. In only one case did a slight infection develop; five months later a small sequestrum was removed and the existing fistula was closed.

Open Medullary Nailing in Cases of Malunion or Nonunion of the Femur. In cases of malunion or nonunion, medullary nailing represents a great advance, because no external support is necessary and the atrophic muscles and joints with limited motion do not need to be immobilized further.

Contraindications for medullary nailing are found (1) in an unfavorable general condition, (2) in osteotomies in patients over 50, (3) in nonunions in patients over 60, (4) in patients under 16 years old, because of the danger of acute osteomyelitis, (5) in infections of the bone and the skin, and (6) with enlarged ossifications of the marrow cavity due to old callus formation. Fistulae should have been closed for from 6 months to one year. All scars, especially when

adherent to the bone, should have been excised previously. Medullary nailing should be performed only after the new scar has become firm and is easily movable on the base; usually this takes about 2 or 3 months.

If shortening of more than 3 centimeters is present, it is very difficult to reduce this during operation, because the muscles are contracted. If an attempt is made to equalize greater shortenings by medullary nailing, severe vessel and nerve disturbances may occur as the result of the sudden tension, and wound infection may arise in the torn tissue. Therefore, the shortening must be corrected prior to medullary nailing. If the callus is not yet solid, the osteoclast may be used. If the callus is solid, the bone is cut with the chisel or the electric saw, if possible, in the old fracture site. With nonunion, the solid connections of the fragments are loosened by bending them over a wedge or with the osteoclast. If the inflammation of infected fractures does not flare up, it probably will not recur after the medullary nailing. Skeletal traction with adequate weight is next applied. After length has been restored, the medullary nailing can be performed. In the case of a closed osteoclasis, this is generally after one week; in the case of an osteotomy, about 3 to 4 weeks should pass.

The medullary nailing is performed with the patient in the lateral position, by the use of a sterile tourniquet. After the fragments have been freed, a longitudinal mark, from 5 to 6 centimeters long and from one to two millimeters deep, is cut into the bone with a small gouge, so that the amount of rotation can be determined. With angulation a corresponding wedge must be sawed, so that the fragments will touch each other exactly. The closed marrow cavity is opened with the awl or the gouge. In more recent cases, the authors have always bridged the fracture site with a piece of removed callus, a bone graft, or chips. The operation continues as for an open fracture, precautions against shock being observed.

Shortening of the Uninvolved Extremity by Medullary Nailing. If an unusual amount of shortening is present and the bone is not suitable for lengthening, only the angulation of the injured limb is corrected. After the patient has completely recovered from the first operation, the sound femur is shortened to equal the length of the broken femur. This should not exceed 8 or 9 centimeters, because of the difficulty in accommodation of the muscles.

After application of a sterile tourniquet, the sound femur is exposed above the middle third. A longitudinal marker, adequate to indicate rotation of the fragments, is chiseled out. Then the bone is sawed through transversely at the edge of the upper and middle thirds, a Gigli saw being used. The distal fragment is elevated and the correct length of bone is removed. Both saw cuts are thus in the narrow portion of the marrow cavity. To avoid rotation, step-cutting may be used, but transverse cutting is easier. Lately the authors have cut from the resected bone one or two strong grafts to bridge the site of the osteotomy. The operation then is continued as for an open fracture.

The authors consider that at present medullary nailing by the method of Kuntscher is the best treatment for transverse closed fractures, for open fractures, and for most of the osteotomies and nonunions of the shaft of the femur, if suitable equipment is available. The union of the fragments is so firm that the patient can walk without additional fixation after the wound has healed, that is,

in two or three weeks. Thus muscle atrophy and stiffness can be almost entirely prevented. With closed medullary nailing, the danger of infection is slight, because only a small incision is made apart from the fracture site. With open medullary nailing, the danger of infection is reduced by exact immobilization. The authors also use medullary nailing for closed transverse fractures in the middle third of the shaft of the humerus. Medullary nailing is a technically difficult procedure and should, therefore, be done only in specially equipped hospitals. (J. Bone and Joint Surg., April '49)

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The Treatment of Acute Brucellosis with Aureomycin: Studies with multiple strains of brucella including both Brucella abortus and Brucella suis indicated that these organisms are sensitive to the antibacterial action of aureomycin in vitro. From 0.25 to 2.0 micrograms of aureomycin per milliliter of medium completely inhibited growth of 11 strains of brucella during the first 72 hours of incubation.

During the period from May to November 1948, five patients having blood cultures positive for brucella organisms and who had been ill from 18 to 103 days were treated with aureomycin. An arbitrary oral dosage of from 2,400 to 3,000 milligrams of aureomycin (from 30 to 60 milligrams per kilogram of body weight) per day was initially administered to all 5 patients except the first. A priming dose of 200 or 250 milligrams was generally given every hour for 3 doses. This same dose was then given every two hours for a varying period ranging from one to 8 days. The antibiotic was then continued in 200 or 250 milligram doses every 3 or 4 hours for a total period of approximately 14 days. The first patient was treated before an oral preparation of aureomycin was available and he received improvised capsules containing 500 milligrams of the crude drug. The latter capsules were given twice a day for 4 days. In all patients except the second, supplemental aureomycin was administered by the intramuscular route. Injections of 40 milligrams of aureomycin dissolved in 2 cc. of a one percent procaine hydrochloride solution were administered every 6, 8, or 12 hours for from 4 to 17 days. The total amount of aureomycin employed varied from 6.7 to 35.3 grams and was administered orally and/or intramuscularly during a period of from 13 to 20 days. Nausea following the administration of aureomycin by mouth was noted in two cases and was accompanied by vomiting in one. Except for the first patient who received the crude aureomycin, this nausea subsided on treatment. Aluminum hydroxide preparations were successfully employed to counteract the local gastric irritation. Intramuscular injections of aureomycin dissolved in one percent procaine solution caused considerable pain and induration at the site of injection. Suppuration was not noted. In one patient from 3 to 4 unformed stools were noted daily on the seventh day of treatment. This patient was receiving a 250 milligram capsule every two hours. These symptoms subsided within two days when an aluminum hydroxide preparation was administered. The dosage of aureomycin had also been reduced to 250 milligrams every 4 hours.

Four of the patients had high fever prior to aureomycin treatment. All became and remained afebrile within 72 hours after the onset of aureomycin therapy. Symptoms markedly diminished with defervescence. In every case headache, fatigue, night sweats, myalgia, chills, arthralgia, and anorexia disappeared during the first week of treatment. When palpable, the liver and spleen

progressively decreased in size under therapy. New embolic and petechial phenomena were not observed after aureomycin was administered. All patients have returned to their former occupations. In each instance a gain in weight followed treatment. This has ranged between from 5 to 40 pounds. There have been no relapses. Three patients have been followed for from 3 to 8 months. The remaining two patients have remained afebrile and asymptomatic for more than two months. In all patients repeated blood cultures for brucella have remained sterile. Before aureomycin treatment, positive cultures for Brucella suis were obtained from the first patient while he was receiving 3 grams of streptomycin and 6 grams of sulfadiazine daily.

Although brucellosis is characterized by an erratic course marked by exacerbations and remissions, it is felt that the results recorded are sufficiently clear to indicate that aureomycin exerts a beneficial influence in this disease. (Bull. Johns Hopkins Hosp., May '49, M. S. Bryer et al.)

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Ulcerative Colitis: The fact that emotional disturbances can produce pathological changes in the colon is now acknowledged. The nervous pathways through which these changes are initiated are probably mainly parasympathetic from the hypothalamus. The motor parasympathetic supply of the small intestine and the proximal part of the colon, up to and including the ascending limb of the splenic flexure, is from the vagus; the rest of the colon and the rectum are supplied by the sacropelvic nerve. Porter points out that in many cases of ulcerative colitis, and especially early ones, the disease remains localized in the section supplied by the sacropelvic nerve; this may be due either to the transmission of more impulses along this nerve or to particular susceptibility of this part of the bowel. One result of parasympathetic stimulation is hypermotility of the small intestine, such as has been observed sometimes by radiologists in patients with ulcerative colitis. This hypermotility causes an increased amount of small-bowel contents to be passed into the colon, together probably with an excess of pancreatic enzymes, which are present in high concentration in the lower end of the ileum.

Porter believes that these enzymes may be responsible for ulceration, partly because gut as seen through a proctoscope resembles the excoriated skin around a fresh ileostomy, and partly because vagotomy has led to improvement in cases in which the disease affects only the area below the vagal supply; but so far there is no evidence of any increase in the trypsin content of the feces. Another possibility is that the bowel wall has a decreased resistance to the enzymes. Normally protection is afforded by the complex carbohydrate, mucin, which is hydrolyzed by lysozyme, an enzyme normally present in the intestinal tract as well as in gastric juice, tears, and nasal mucus; and with ulcerative colitis lysozyme has been found in great excess. Furthermore, the production of lysozyme appears to be under parasympathetic control; Meyer et al. found in 5 patients with peptic ulcer an average fall in lysozyme titre of 44 percent after vagotomy. Thus, parasympathetic overaction may well cause increased production of lysozyme with destruction of mucin, followed by lowered resistance of the bowel wall, this in turn leading to invasion both by tryptic enzymes and by normally innocuous bacteria. Grace et al. (News Letter of 8 April 1949, page 21) have confirmed that in ulcerative colitis the concentration of lysozyme in the

stools is high, and they also discovered that the concentration varied with the activity of the disease; during a remission it was relatively low, while during relapses it rose sharply, the increase sometimes preceding exacerbation of diarrhea. Moreover, the lysozyme concentration was definitely related to the emotional state, being low when the patient was calm and relaxed, and rising in response to stimuli such as unexpressed anger, hostility, and resentment. By contrast emotional stimulation of normal subjects and patients with mild types of diarrhea without ulceration caused only slight and transitory rise in lysozyme concentration. That ulceration per se does not account for the increase in lysozyme was shown by the low concentration found in a patient with ulceration secondary to carcinoma of the colon.

These findings have practical applications. The damping-down of emotional stimuli with phenobarbitone, already widely practiced, is freshly justified. Belladonna, or one of its alkaloids, is also often used, especially when pain is prominent, and routine use may well be advisable. To inactivate the pancreatic enzymes, Porter uses sodium alkyl or lauryl sulphate (both sulphonated fatty alcohols), and Meyer has found that these agents bind and inactivate lysozyme as well; they are best given in enteric-coated pills in doses of from 100 to 200 mg. 3 times a day. Sulphonamides or other antibiotics seldom seem to have much effect on the course of the disease, but a short course of one of them to combat secondary infection of the damaged mucosa seems rational, especially in the more acute type of case. Apart from these drugs, the full medical regimen must include a low-residue, high-calorie, high-protein diet with added vitamins and iron. Blood-transfusion may be necessary to maintain the hemoglobin level, and liver injections 2 or 3 times weekly are sometimes recommended. The psychiatrist's help may be sought when the condition is under control, but Porter believes that premature psychiatric investigation may actually aggravate the bowel lesion.

Failure of medical treatment raises the question of ileostomy, which may sometimes be followed by colectomy. Ileostomy is indicated first in the acute fulminating type of the disease, in which it is done as a last resort and is seldom successful, and secondly in the chronic type in which the illness has pursued a relentless course for several years, with little or no remission or with persistent relapses. These patients are leading miserable lives, unable to work or enjoy social activities; depression and frustration add to the discomforts of their disease. To them ileostomy offers the possibility of return to an almost normal life; but, as McKittrick and Moore, of Boston, observe, they should in fact have experienced this miserable existence before operation is undertaken, for only thus will they know that the benefits of ileostomy outweight its inconveniences. McKittrick and Moore followed up 110 patients with an ileostomy. Of these, 6 had died from other diseases. Of the remaining 104, 88 (84 percent) reported that they were in good health. Maladjustment was commonest in men of poor intelligence who found difficulty in looking after the ileostomy while engaged in outdoor work, and in young unmarried women who could not endure the thought of marriage with such a disability. To the majority, however, this operation brings a new lease on life. (Lancet, 30 April '49)

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Decamethonium Iodide (Bistrimethylammonium Decane Diiodide) in Anesthesia: As a result of the study of a series of polymethylene bistrimethylammonium compounds in 6 different species of animals, at the National Institute for Medical Research, Paton and Zaimis suggested the use of the decane derivative (decamethonium iodide) as a substitute for d-tubocurarine. Because preliminary trials in volunteers proved satisfactory, an investigation into its use in anesthesia has been undertaken by a number of workers on behalf of the anesthetics committee of the Medical Research Council and the Royal Society of Medicine. A full report will be published when this work is completed. The publication of this interim report has been necessitated by the placing of decamethonium iodide on the market.

Decamethonium iodide is a white crystalline salt, easily soluble in water, forming a neutral solution, sterilizable by heat, and stable. The formula is $(CH_3)_3N^+ . (CH_2)_{10} . N^+(CH_3)_3 . 2I^-$. It is a simple compound chemically, cheap, and easy to prepare in a pure state. It is miscible with the alkaloids, with procaine, and with thiopentone. It is nonirritant and may be injected into any tissue without sign of reaction. Injection of small doses into animals causes a neuromuscular block, which appears to affect skeletal more than respiratory muscles. The block is not affected by anticholinesterases such as neostigmine, but is antagonized by pentamethonium iodide (which is virtually devoid of curarising activity), probably through competitive inhibition. Decamethonium iodide has much less activity in liberating histamine or heparin and has less activity in paralyzing autonomic ganglia than has d-tubocurarine. Experiments on animals show a wide species variation of potency. It is excreted, largely, in the urine. The fate of the remaining fraction is not yet known.

Decamethonium iodide has been used at the Westminister Hospital in 150 operations of many different types, most of them being laparotomies, on patients from 15 to 83 years of age. Preliminary trials have established that it is in every way a safe and satisfactory substitute for d-tubocurarine, and it is now being used in unselected cases. The total dose has been from 1.5 to 10 mg. There is no clear relationship between effective dose and body-weight. A single intravenous injection of 3 mg. in light surgical anesthesia produces, in most patients, good muscular relaxation without unduly depressing respiration. This dose may therefore be taken as approximately equivalent to 15 mg. of d-tubocurarine chloride. An injection of 4 mg. often, and of 5 mg. almost invariably, produces apnea lasting usually 10, occasionally 20, minutes. Its action is relatively evanescent and therefore, perhaps, more controllable; further injections are made at intervals of from 10 to 40 minutes, as required; the dose depends on the preceding interval; after 40 minutes a further 3 mg. will probably be necessary. A relaxant dose can be given for closing the peritoneum after laparotomy, with the assurance that adequate spontaneous respiration will be present by the time the operation has been completed. Pentamethonium iodide, in a dose 10 times that of decamethonium iodide, has proved an effective antidote. It produces a powerful block of autonomic ganglia in animals. Like tetraethylammonium bromide, it may cause a fall of blood pressure in man. The author and his co-workers have not found its use necessary in anesthetic practice.

Thoracic and abdominal breathing fail and recover together. It has been noticed in some cases, that the tone of the abdominal flank muscles persists as

long as does respiration. In such cases it may, rarely, be necessary to paralyze respiration before sufficient relaxation can be secured for peritoneal closure. In two patients, neither of whom was intubated a slight expiratory wheeze was detected. There is no reason to suppose that decamethonium iodide will have any effect on the production or prevention of bronchospasm. Davies and Lewis, investigating the use of relaxants in electroconvulsive therapy, twice met with severe bronchospasm in one patient with d-tubocurarine, but this did not appear when decamethonium iodide was substituted. It has been used successfully in the management of intrathoracic operations with controlled respiration. It seems to act similarly to d-tubocurarine in reducing laryngeal muscular irritability and has proved effective in facilitating tracheal intubation, and, with thiopentone, for bronchoscopy and esophagoscopy. There appears to be no direct effect on the cardiovascular system, even with relatively large doses. It had been anticipated that, owing to the absence of any significant block of autonomic ganglia, traumatic shock might appear more often than with d-tubocurarine in severe operations under only a light screen of general anesthesia. In practice it has been found that though, as expected, the blood pressure has fluctuated more widely, the general level has been well maintained. Bleeding from cut surfaces is, perhaps, less than with d-tubocurarine. Cesarean sections have been undertaken with diffidence, because the relatively small molecule of decamethonium iodide might be expected to cross the placental barrier. With not more than 3 mg., injected intravenously at least 10 minutes before delivery, with light nitrous oxide-ether anesthesia, the results have been entirely satisfactory. The uterus has contracted well with the routine intra-uterine injection of ergometrine and pituitrin. Denny and Scurr have obtained satisfactory relaxation of the uterus for difficult external versions using an injection of 3 mg. immediately after the induction of light nitrous oxide-ether anesthesia. The patients recover consciousness within a few minutes.

Postoperatively, some patients who have rapidly recovered consciousness have complained of slight giddiness, lightheadedness, or headache. Vomiting, usually slight, has occurred in well under 25 percent of patients in a series including a majority of major abdominal operations. There has been one case of ileus with peritonitis; abdominal distension is, otherwise, less than usual. Postoperative pulmonary collapse seems to be considerably less frequent than after d-tubocurarine chloride, though it is not yet possible to be certain of this. All of five patients who developed lobar collapse had respiratory paralysis during the course of operation; inadequate pulmonary ventilation may have been a contributory factor. All except one (herniorrhaphy) had a cuffed tracheal tube, and all had thiopentone and cyclopropane. As many as 9 percent have had retention of urine for 24 hours, recovering spontaneously. The significance, if any, of this must await further investigation. There have been no cardiovascular complications attributable to the anesthetic.

All the common anesthetic agents have been used, alone or in combination, with no obvious difference in effect. Provided the depth of anesthesia is sufficient to prevent any obvious reaction to surgical trauma, the muscular relaxation produced by decamethonium iodide appears to be maximal. Inadequate relaxation is improved only at depths in which the anesthetic agent alone might be expected to produce a similar effect. In animals, ether appears to reduce the relaxant effect and increase the tendency to respiratory paralysis. A mixture of decamethonium iodide 4 mg. with thiopentone 1 Gm. has been used successfully. There seems to

be no operation which could not be undertaken, if necessary, with this mixture, provided there is available some means of inflating the patient's lungs with air. The simplicity and portability of the necessary apparatus are attractive, particularly in such conditions as might be found on military service.

Decamethonium iodide is marketed, in ampoules of a solution containing 2 mg. per ml., by Messrs. Allen and Hanburys ('Eulissin') and by Messrs. Burroughs Wellcome ('Syncurine'), who have supplied the drug for investigation by the anesthetics committee. (Lancet, 7 May '49, G. Organe)

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Effects of Decamethonium Iodide (C10) on Respiration and on Induced Convulsions in Man: The action of bistrimethylammonium decane diiodide (C10), now known as decamethonium iodide, in producing neuromuscular block in animals and its effect in a small number of human subjects pointed to its clinical use for the same purposes served by curare. It appeared from the preliminary studies that C10 had the advantage over curare that it spared the respiratory muscles. The investigation here reported (carried out by arrangement with the Medical Research Council) was concerned with collecting further evidence on this point and with determining whether C10 is suitable for reducing the force, and therefore the risks, of convulsions that are induced in the treatment of certain mental disorders.

Eighteen patients with a depressive illness were selected; all were judged likely to benefit from electrically induced convulsions, and all were free from physical disease. There were 7 men and 11 women whose ages ranged from 19 to 59. Each had a normal electrocardiogram. They were given d-tubocurarine chloride (A) 15 mg. (1.5 ml.) intravenously on the first occasion, and C10 3 mg. (3 ml.) intravenously on the second occasion three days later; thereafter, the order of injection was C10, A, A, C10, C10, A, to preclude effects of suggestion. The patients arrived fasting, having received atropine sulphate gr. 1/100 subcutaneously 45 minutes earlier in order to lessen salivation during and after the fit. The injection of the C10 or the d-tubocurarine chloride took 15 seconds. After the effect of the first injection of C10 had been observed, the dose was varied, to produce an optimum modification of the fit and one of the same degree as a given dose of d-tubocurarine chloride would effect in the same patient. As the maximum paralyzant effect of the drugs was manifested in the fourth minute from the start of the injection, the electrical stimulus was applied (from a MacPhail-Strauss machine) at the end of 4 and 1/2 minutes. The quantity of electricity delivered was kept constant throughout the series of observations.

The effects of C10 were not distinguishable by direct observation from those of d-tubocurarine chloride, either in respect of the pareses and paralyses induced or the characteristics of the modified convulsion. The eyelids, facial muscles, and neck muscles were early affected; the small muscles of the hand were demonstrably weakened before the larger muscles moving the proximal joints. Writhing movements of the arm were still possible after hand-grip had been lost. The voice became a whisper, and then inaudible; this was somewhat more readily effected by d-tubocurarine chloride than by an otherwise equivalent

dose of C10. The bigger the dose of C10, the greater the paralyzing effect. The largest dose given of C10 was 5.5 mg. Patients differed from one another in the dose required to produce a severe effect and this did not depend on their weight; 4 mg. of C10 produced a greater effect in a man weighing 173 lb. than the same dose in another man weighing 111 lb. Age and emotional causes, especially fear, seemed to be of some importance in determining the severity of response.

It was not possible, from the degree of weakness produced during the 4 minutes after the injection, to predict with confidence how great would be the modification of the induced convulsion, though as a rule there was close correspondence. When the modification was maximal, nothing but a few clonic twitches around the eyes and a twitch of the platysma attested the occurrence of a convulsion; so complete a modification occurred only twice, and was not aimed at. All the patients recovered from the effects of the drug and of the induced convulsions sufficiently to walk from the room, with slight assistance, within half an hour after the injection. In their written accounts, no patient distinguished between the effect of the two drugs. Those who could remember events just before the convulsion described unpleasant sensations, loss of power in their limbs, and difficulty in breathing.

Because several patients of the foregoing group complained of the unpleasant sensations produced by C10, as by d-tubocurarine chloride, it was administered to a larger series in combination with thiopentone sodium. One hundred and fifty administrations of C10 with thiopentone sodium have now been given to 40 patients without any misadventure. The patients did not report any disagreeable recollections of the period between the injection and their awakening from the postconvulsive state. A patient, who had been given atropine sulphate gr. 1/100 45 minutes in advance of the treatment, received an intravenous injection of thiopentone, 0.25 Gm. in 5 ml. solution, mixed with 3 mg. of C10 (3 ml.). The two drugs are freely miscible. A dose of 30 mg. of C5 (the antidote to C10) was kept in a syringe during each treatment session but the need for its use did not arise.

The mixture of thiopentone and C10 was injected with the precautions advocated for all thiopentone injections by Macintosh and Heyworth. The usual effect was immediate sleep. The patient's head was then turned to one side and his jaw held forward to prevent his tongue falling back. Just before the induction of the fit, 3 and 1/2 minutes after the injection (best measured by a stop-watch), the patient's head was restored to the middle position, and a rubber gag introduced between his teeth. No physical restraint of any kind was used, and no pillow put under the patient's back.

When the fit began, the rubber gag was removed and in its place a lubricated Guedel's airway of suitable size was immediately introduced. If breathing was not satisfactorily restored spontaneously after the fit, controlled respiration was instituted, by means of a McKesson face-piece connected through a three-way valve to a rebreathing bag, which in turn was connected through a flowmeter to an oxygen cylinder. With the patient's head to one side, the face-piece was held firmly to the face in a gas-tight fitting by the employment of one hand, the little finger of which from behind the angle of the jaw maintained the jaw forward, leaving the other hand free to compress the bag. The breathing in such cases became satisfactory after from a minute to a minute and a half, and the patient

was then removed to the recovery room. The airway was not removed until the patient had regained control of his tongue. Most patients were able to walk out of the recovery room, with slight assistance, within half an hour.

The dose was determined after observing the effect of the first injection of 3 mg. of C10, with thiopentone. In some patients it could be lessened, in others it had to be increased, but never beyond 5 mg. It was in all patients possible to obtain a ++ or +++ modification of the convulsion. In those patients who had a physical disability which made it essential that the convulsion should be very much modified in order to avoid risk of damage, an initial dose of 4 mg. of C10 was given; the dose was subsequently reduced when it proved needlessly large. This procedure was followed with two patients, of whom one had an ankylosed elbow and the other a history of slipped cervical disc.

The advantages of C10 over d-tubocurarine chloride for general use in convulsant therapy would from this series of observations appear to be:

(1) It has no untoward effects. Severe and alarming bronchospasm was produced by d-tubocurarine chloride in a patient on the two occasions on which it was given to him, but he had no such effect from C10 repeatedly administered, nor did any other patient develop this symptom after C10.

(2) C10 is readily miscible with thiopentone, whereas most preparations of curarine are not.

(3) It is simple to prepare, and cheap.

(Lancet, 7 May '49, D. L. Davies and A. Lewis)

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The Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients Suffering with Chronic Suppurative Infection: During a study of prolonged suppurative infection in 91 young men, the authors observed reticulocytosis, which was followed by increases in hematocrit and hemoglobin values, in the blood of patients being given cobaltous chloride by mouth. These findings were not completely unexpected because it has long been known that cobalt is a hematopoietic agent effective in deficient and in healthy animals. Therapy with cobalt apparently stimulates red-cell production in children, as well as in adults, and also protects animals from developing anemia when sterile suppuration is induced experimentally. As far as the authors are aware, cobalt has not been employed in the U. S. A. in the treatment of patients ill with chronic sepsis. This report, therefore, presents observations on the blood of 9 patients suffering with prolonged suppurative infections who were treated for from 2 to 11 weeks by the daily oral administration of from 20 to 60 mg. of cobaltous chloride.

The average age of the 9 male patients selected for this study was 25 years (the oldest was 36 and the youngest 18). Three patients had been injured by automobiles, and 6 had been wounded by bullets or fragments from land mines. When first selected for this study these patients had already spent an average of 28 months in hospitals because of chronic osteomyelitis or chronic soft-tissue suppuration. At the time of injury and thereafter all patients had received adequate therapy with blood and blood substitutes and, in addition, had been treated with sulfonamide derivatives (usually sulfadiazine), penicillin, and streptomycin. Reconstructive surgical procedures had been carried out on

numerous occasions in all patients. When first observed by the authors all patients showed evidence of chronic sepsis as judged by drainage of pus from wounds, pyuria, continued fever, or radiographic evidence of bone sequestra. There was no clinical evidence of vitamin or protein deficiencies although all patients had lost weight. The red-cell sedimentation rate was increased, and in all cases cultures of organisms were obtained from sites of apparent sepsis. The organisms were identified and were usually found to be resistant to penicillin or streptomycin. In these patients plasma iron levels were low, and plasma copper levels were increased. Control measurements of blood volumes, hemoglobin levels, hematocrit values and cell counts were made on at least two occasions before therapy was instituted.

After the patients had been observed during the control period they were treated with from 20 to 60 mg. of cobaltous chloride in tablet form taken orally each day after meals. Treatment was continued for 11 weeks in 4 patients, for 4 weeks in a second group of 4 patients, and for two weeks in one patient. During this time none of the patients received transfusions or therapy with other hematopoietic agents. Two patients whose wounds were infected with penicillin-fast organisms, had previously been given injections of penicillin on numerous occasions without clinical effect, and were again treated with penicillin while taking cobalt. The penicillin was administered at a time when reticulocyte response had already been observed and, in the authors' opinion, did not affect the course of the illness.

Before treatment, red-cell counts, reticulocyte counts, hemoglobin concentrations, hematocrit levels and total circulating hemoglobin were constant and reduced below the levels found in otherwise normal but bedridden control subjects. The significant deviations from the normal were in measurements of total circulating hemoglobin, which was reduced on the average 26 percent below levels found in the controls. After treatment with cobaltous chloride, reticulocyte responses were observed in each of the 9 patients. These occurred as early as the fourth day and continued throughout therapy. The maximal reticulocyte percentages were usually observed between the sixth and tenth days, and did not exceed 5 percent in any case. A steady increase in red-cell counts, hematocrit levels and total circulating hemoglobin followed the reticulocyte response. In one patient considerable increases in blood values occurred during the first 8 weeks of treatment with cobalt; an extensive sequestrectomy of the femur was performed during the ninth week of therapy, and, during the next two weeks while he was still taking cobalt, the total circulating hemoglobin, red-cell count and hematocrit levels returned to pretherapy levels. The average blood values of the 9 patients reached normal levels after cobalt therapy. There was a significant change in the blood volume, owing in the main to a 30 percent increase in the circulating red-cell mass, the plasma volume changing but slightly. The total circulating hemoglobin increased, on the average, 29 percent above the levels before therapy. White-cell counts and differential cell counts showed few changes and mean corpuscular volume altered but slightly. In 4 patients, in whom measurements were made before and after treatment with cobalt, plasma iron and copper levels were not affected by cobalt therapy.

During therapy with cobalt slight loss of appetite was observed in 2 patients. All patients developed a dusky discoloration of the skin, especially marked below the eyelids. This change in the color of the skin was probably

due to the dye T-1824 used for measuring blood volumes, but it may have been an effect of cobalt therapy. No other abnormal signs or symptoms of cobalt toxicity were observed.

Preliminary observations on the effect of cobalt on the blood of normal and anemic persons have been reported in the German literature by Weissbecker and Maurer. They state that after daily oral therapy with 500 mg. of cobalt chloride a reticulocyte peak occurred on the third day, and thereafter increases in erythrocyte, hemoglobin, and hematocrit values occurred. Mean corpuscular volume and red-cell diameter decreased. The Price-Jones curve shifted to the left, and its base broadened. Osmotic resistance, serum bilirubin, white-cell count, and differential cell count remained unchanged. Blood volume increased, but plasma volume remained steady. In normal adults a true polycythemia developed, and blood levels returned to normal in patients anemic from blood loss. Weissbecker and Maurer observed toxic symptoms in themselves and in their patients. These consisted of nausea, vomiting, diarrhea, and reddening of the face and extremities, which was accompanied by hot flushes. In the anemia of chronic infection adequate responses occurred in some patients. However, in those who had severe chronic infection the effects of cobalt therapy were small and consisted of reticulocyte responses and bone-marrow maturation. Weissbecker and Maurer state that in patients with chronic infection the available serum iron was an index of ability to regenerate blood. In the 9 patients reported upon above, plasma iron was reduced but not to very low levels. These patients were well fed. Their nutritional status regarding protein and vitamins was good even after two years in the hospital. The German authors make no comment on the nutritional status of their patients ill with chronic sepsis, but it is likely that they were not as well fed as these 9 patients. It is possible that nutritional disturbances in some patients account for failure to respond maximally to cobalt.

The mode of action of cobalt on the blood remains a mystery. Specific effects of cobalt therapy on anemia are seen in cattle and sheep that graze on grass deficient in this trace element, and good hematopoietic responses occur after therapy with very small amounts (0.1 mg.) of cobalt. Castle, in a recent talk, suggested that cobalt-deficient animals are really suffering from vitamin B_{12} deficiency. He speculated that normally bacteria in the rumen of cattle synthesize vitamin B_{12}, a cobalt-containing organic substance, and that the vitamin exerts a specific effect on hematopoiesis after it is absorbed. He also suggested that when the animals live on cobalt-deficient feed the intestinal flora are not able to form the vitamin. Consequently, the animals develop vitamin B_{12} deficiency and become anemic.

It does not seem possible that cobalt exerts a specific effect on the blood in patients with chronic infections. Their anemia is refractory to therapy with liver, which contains vitamin B_{12}, and they require relatively large quantities of cobalt for erythropoiesis to take place. It is more likely that the hematopoiesis that follows massive cobalt therapy is due to a nonspecific stimulus to the bone marrow. This may be a consequence of generalized tissue anoxia or may follow impaired oxygen transfer from the blood to the bone marrow. There is good evidence in the literature that cobalt inhibits the respiration of micro-organisms as well as animal tissues and tumors and that it does so by inhibiting -SH groups of enzyme systems. Oral therapy with sulfur-containing amino acids, such as cysteine and also to a lesser extent with histidine, inhibits the effects of cobalt

in producing polycythemia in rats, and parenteral cobalt-cysteine complexes are also unable to produce polycythemia. Ascorbic acid, a reducing substance, also inhibits the effects of cobalt in producing polycythemia in rabbits and dogs.

Inasmuch as the patients developed a blue discoloration of the skin, the authors speculated that it and the bone-marrow anoxia were due to methemoglobin, produced by cobalt interference with the normal reconversion in the red blood cell of methemoglobin to hemoglobin, a reducing mechanism that is continuously taking place in the blood. The authors therefore examined the blood of 4 patients spectroscopically but were not able to detect methemoglobin after therapy with cobalt. The mechanism of cobalt activity in patients with chronic infection therefore remains unexplained and requires further study. (New England J. Med., 12 May '49, J. C. Robinson et al.)

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Erythropoietic Effect of Cobalt in Patients with or without Anemia: The purpose of this study was to determine the erythropoietic effect of cobalt first in hematologically normal patients, then, especially because of the apparently successful results of Kleinberg and his associates in rabbits poisoned with benzol, it was proposed to extend the observations to patients with anemias refractory to recognized forms of treatment. If effective in causing increased erythropoiesis, cobalt therapy might be useful as a substitute, at least in part, for the repeated transfusions required in the treatment of such patients.

Cobaltous chloride ($COCl_2.6\ H_2O$) in the form of a 2.5 percent aqueous solution was administered to 61 patients. Unless otherwise indicated, a dose of 4 cc., containing 100 mg. of cobaltous chloride, was given orally, thrice daily after meals, well diluted with water.

In 17 patients without anemia the daily oral administration of 300 mg. of cobaltous chloride produced slight reticulocyte responses in all within a week. Of 10 patients given the therapeutic agent for over 4 weeks, moderate increases in red blood cells, hemoglobin and hematocrit were observed in all but one.

Similar doses of cobaltous chloride were given for more than 4 weeks to 20 patients with various types of anemia refractory to other forms of therapy. In 2 of 5 patients with moderate anemia associated with chronic infections, in one of two patients with hypochromic anemia associated with inoperable carcinoma of the stomach and in one patient with familial microcytic (Cooley's trait) anemia, definite reticulocyte responses and rises in red-cell, hemoglobin and hematocrit values were observed.

In only 3 of 10 patients in the lymphoma group,(2 with reticulum-cell sarcoma and one with chronic lymphatic leukemia) was even suggestive evidence of ability to maintain higher erythrocyte and hemoglobin levels obtained.

In none of 5 patients with refractory anemia and hypercellular bone marrow was erythropoiesis detectably affected. In one patient with the anemia of cirrhosis of the liver no response was obtained in an adequate trial. In two patients with anemia associated with chronic renal failure, given the drug for only a few days, no evidence of a reticulocyte response was noted.

Red blood cells produced by a patient during 11 weeks of treatment with cobalt contained spectrophotometrically normal oxyhemoglobin and survived normally when transfused into another patient.

The toxicity of cobalt at dosage levels capable of causing polycythemia is difficult to estimate from reports in the literature. When administered orally, cobalt salts are largely excreted in the feces, and even the portion absorbed from the intestinal tract is mostly lost in the urine within a few days. Thus, at the height of the polycythemia produced in rats, only from 40 to 50 micrograms of cobalt may be found in the entire body of the animal. When cobalt salts are injected elimination is largely in the urine and bile, but as much as 5 percent may be retained by the tissues 10 days later. Presumably as a result of the poor absorption of the cobalt salts, the production of significant polycythemia in the adult rat requires the daily oral administration of about 40 mg. per kilogram of body weight, in contrast to only 2.5 mg. of cobaltous chloride daily by injection.

Early observations showed that when given orally in sufficient dosage to dogs cobalt salts caused irritation of the intestine and death in convulsions. Ten milligrams killed a frog in half an hour, and 300 mg. was fatal to a rabbit in 3 hours. In dogs from 200 to 300 mg. per kilogram of body weight caused vomiting, diarrhea and sometimes acute nephritis. With larger doses, dyspnea and a fall of blood pressure appear, and death may result from cardiac paralysis. Until a certain daily oral dosage level is reached, which varies in different species and individuals, there may be no signs of toxicity and then only a poor appetite, which promptly improves with the discontinuance of the cobalt. In the opinion of LeGoff, who has studied the subject of cobalt toxicity both in animals and in man, cobalt is not more dangerous than iron, the immediate toxic actions of which it seems to imitate. The subcutaneous injection of from 10 to 50 mg. of cobaltous chloride in human subjects caused a sensation of heat in the face and a fall of blood pressure. To one patient LeGoff gave 90 mg. daily orally for a hundred days, and to another 122 subcutaneous injections of 25 mg. each during a period of 3 years, without apparent harm.

The chief manifestations of toxicity from the oral administration of cobalt in the authors' experience were, as reported by others, referable to the alimentary tract, namely, anorexia, heartburn, nausea, and vomiting. In many patients receiving 300 mg. daily these symptoms were minimal or absent, but in some they were a very real obstacle. The promptness and consistency with

which each of 12 patients with pernicious anemia in complete remission experienced severe symptoms referable to the gastro-intestinal tract suggest that the typical achlorhydria or rapid emptying time of the stomach was responsible and may occasionally condition similar undesirable side effects in other patients.

A patient with chronic lymphatic leukemia was given an intravenous injection of 50 mg. of cobaltous chloride dissolved in 250 cc. of sterile physiologic saline solution on 16 occasions during a period of 37 days. Whenever a given rate of infusion was exceeded, he experienced burning sensations and flushing of the face. However, if two hours were allowed to elapse for the entire injection, little difficulty was encountered. On one occasion when 75 mg. of cobaltous chloride was given to this patient intravenously, an episode of nausea, vomiting, and bone pain occurred. No pathologic changes appeared in the urine of this patient or of any of the other patients during the period of cobalt administration.

Two patients, one with reticulum-cell sarcoma and the other with giant-follicle lymphoma, after being under treatment continuously with cobalt for one and two months, respectively, complained of severe substernal pain, which they attributed to the drug. In the first patient, who was 65 years of age, the pain disappeared when cobalt administration was stopped for a few days, only to return when the therapy was resumed. An electrocardiogram was normal at the time, but when autopsy was performed 4 months later, an old septal infarct was found. In the second patient, aged 58 years, the electrocardiogram was consistent with myocardial infarction. It seems doubtful that the cobalt administration was responsible for the production of the infarct, but it is understandable that the drug could give rise to symptoms in patients who probably already possessed an insufficient blood supply to the myocardium, especially if the fundamental action of cobalt salts is to interfere with intracellular respiration.

As with any therapeutic agent, the possibility of injury from cobalt must be balanced against the urgency of the need for the drug. With cobalt there is perhaps little evidence of toxicity, at least after oral administration, other than irritation of the alimentary tract. However, the authors have found that there is also little probability of benefit in severe types of anemia otherwise not amenable to therapy. In mild anemias associated with chronic infections, the benefit from the slight increase in hemoglobin that can be confidently expected may well be offset by the loss of appetite due to the drug. For these reasons, the clinical use of cobalt should probably be confined to use in cases of anemia in which other methods of treatment are clearly of no value. Thus, there is no indication for the use of cobalt as an adjuvant to liver extract or iron therapy. Moreover, it is likely that by critical determination of the daily level of reticulocytes during a period no longer than a week, the probable usefulness of the drug for a longer time in any given patient can be assessed. (New England J. Med., 12 May '49, L. Berk et al.)

Report of the Species Specificity of Agene Toxicity: For many years the syndrome of ataxia, running fits, hysterical states, and convulsions has been recognized in dogs. Within the last two years, evidence has indicated that wheat-protein which has been treated by nitrogen trichloride (agene) is the causative agent. This was discovered by Mellanby, who reported that dogs fed an adequate diet containing flour treated with agene developed the syndrome; untreated flour proved harmless. Other investigators have confirmed Mellanby's observations and further studies have shown the toxin to be the result of the interaction of wheat and other proteins with agene.

The necessity for further investigation of its effects on man became more apparent as the animal experiments proceeded. Because the general population has consumed commercially treated flour for a long time without the appearance of the syndrome, and previous investigations have indicated that human subjects of various age groups show no impairment after ingesting moderate amounts of agenized materials, it seemed desirable to test its toxicity on patients subject to epileptic seizures.

Regular unbleached commercial flour was experimentally treated with agene until the agene level was from 150 to 300 Gm. of nitrogen trichloride per 100 lbs. of flour. This was then baked into bread and cookies. Identical unbleached commercial flour was also baked into bread and cookies for the control ration. The control and experimentally treated baked products were tested on dogs, cats, monkeys, and human beings.

It was found that the ingestion of over one half of the initial body weight of heavily agenized bread and cookies had no apparent ill-effect on three patients with epilepsy. No demonstrable changes could be detected in the EEG; no abnormality in the concentration and albumin content of the urine, as has been reported in the dog, was seen; no alteration of the NPN, urea nitrogen, creatine, fasting blood sugar; no changes in the hematogram or the cerebrospinal fluid; and no abnormality of the EKG. There was no increase of seizure activity over that present when the patients were on the untreated control diet. No gross psychological, psychiatric, nutritional, or neurological defects resulted from the ingestion of the experimental diet. When given 30 percent CO_2 + 70 percent O_2 to inhale just prior to the discontinuation of the experimental diet, no grand mal convulsions or seizure discharges were observed.

The cats, monkeys, and dogs were fed the identical control and experimental rations as were the patients. Every dog fed the experimental diet showed severe signs of toxicity within 18 hours. Usually only one feeding was necessary. If the animal was allowed to feed again, he died in status epilepticus. Thus, for dogs, the agenized material used in this study was invariably lethal if a quantity equal to 0.04 of the animal's body weight was ingested. All 20 dogs used showed the classical signs of intoxication with agenized material. Their abnormal

EEGs could be made worse and seizures induced if a respiratory mixture of 30 percent CO_2 + 70 percent O_2 was administered.

The 12 cats and 4 monkeys, on the other hand, showed no gross abnormalities after ingestion of agenized baked products even in amounts equal to one half their body weight. No tremors or convulsions were noted and the response to carbon dioxide inhalation did not produce seizure activity, although in one cat the EEG did show a few high voltage slow waves after inhalation of 30 percent CO_2 + 70 percent O_2.

The human beings, cats, and monkeys gained greatly in weight on the diet of agenized wheat products. The present results are in accord with previous studies indicating that man is not injured by diets containing agenized material. In the present study, although the dose of agenized material was greater than has been used heretofore, the patients were unharmed by this amount of agenized bread and cookies which, when adjusted for body weight was 10 times as great as the lethal dose for dogs. Next to dogs, it has been found that rabbits and ferrets are most susceptible to agene toxicity. On the other hand, rats, guinea pigs, hamsters, mice and chickens, as well as man, show no evidence of susceptibility. Monkeys and cats, as mentioned, vary in their reactivity. It would appear that susceptibility to toxic effects from ingested agenized protein is species specific. It seems difficult to conceive of any other explanation for the extremely different responses of man and dog. It remains to be seen whether man has a specific detoxification process for the toxic material, or whether his insusceptibility is the result of enzyme systems distinctly different from those of the dog.

Even dogs seem to be able to ingest 0.1 Gm. of NCl_3 plus reacted gluten per kg. per dog without toxic effects. Only when this level is exceeded do the typical abnormalities appear. There is no experimental evidence to explain this low threshold. The nonsusceptibility of other species might be the result of a higher excretion or destruction threshold among other inherent differences. (Medical Nutrition Lab., Chicago, Ill., Rep. No. 46, 21 Feb '49, G. H. Pollock)

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Mel B in the Treatment of Human Trypanosomiasis: For practical therapeutic purposes, the etiological entity of human Trypanosomiasis presents two entirely different aspects due to the fact that the classical drugs, satisfactory in the first stage of the disease, are inactive in the second stage, and vice versa. In the so-called first stage of human sleeping sickness, in which the spread of the trypanosomes is limited to blood and lymph glands, hundreds of the approximately 12,000 trypanocidal arsenicals developed since Ehrlich's times and at least a dozen of the metal-free urea and amidine derivatives are capable of achieving definite cures. Three of these drugs, namely, atoxyl, Bayer 205, and pentamidine are at present in use for the routine mass treatment of the

hemato-lymphatic stage by the various African Sleeping Sickness Services. Of these, pentamidine seems to offer maximum advantages, as it not only cures first-stage sleeping sickness within 10 days, but also confers a long lasting resistance to re-infection. Unfortunately, all the drugs mentioned so far do not penetrate into the cerebrospinal fluid and are therefore of no therapeutic value in the so-called second or meningo-encephalitis stage of sleeping sickness. In this stage, only one drug, tryparsamide, is so far of any help. Tryparsamide has two drawbacks in that (1) it is unsatisfactory as a trypanocidal agent in the hemato-lymphatic stage of the disease and (2) its usefulness in the second stage becomes more and more curtailed, as the number of tryparsamide-fast strains of trypanosomes increases all over Africa.

In French West Africa, with a total population of 16 millions, the Sleeping Sickness Service has examined in 1946, 4.6 million persons, detecting over 50,000 new cases of which 60 percent were found to be in the second stage. The Sleeping Sickness Service of the Belgian Congo reports that 80 percent of all second stage cases detected are tryparsamide resistant.

It follows that the choice of the appropriate drug for the treatment of sleeping sickness must be based on a careful differential diagnosis of the stage of the disease, i.e., that all persons found to carry trypanosomes in glands and/or blood must be submitted to spinal puncture. The scope of the practical consequences, as to organization and personnel, evolving from this situation, can be appreciated by the fact that the Sleeping Sickness Service of French West Africa performed over 50,000 spinal punctures in the course of the year 1946. It is a further handicap for the organization of mass treatment that two different schemes of treatment have to be established, involving widely different time tables. The treatment of the first stage with pentamidine can be completed within 10 days, but the tryparsamide treatment of the second stage, with or without addition of another drug, such as Bayer 205, takes a minimum of 10 weeks, and routinely 3 such courses of 10 weeks are applied at intervals of 3 months which brings the duration of the treatment up to one year.

This situation points to the need for a drug which would be curative, by a short course of treatment, indiscriminately in all stages of sleeping sickness. A solution to the problem seems to have been achieved with p-melaminylphenylarsenoxide (Melarsen Oxide). Sleeping sickness of all stages, including advanced second-stage cases, have been cured with a melarsen oxide treatment consisting of 2 series of 7 intravenous daily injections of 1.5 milligrams per kg. of body weight each, the 2 series being separated by a rest period of one month. These results have been controlled up to 10 months after treatment.

Further research in the series of melaminyl arsenicals in the author's laboratory has led to a new compound, designated "Mel B," which is an alkyl mercapto derivative of melaminylphenylarsenoxide containing trivalent arsenic. Mel B is tolerated at significantly higher doses than melarsen oxide. This allows doubling the individual dose and shortening of the duration of treatment.

Treatment with Mel B was carried out in collaboration with the Sleeping Sickness Service of French West Africa in 50 previously untreated patients with advanced second-stage sleeping sickness due to Trypanosoma gambiense and transmitted by Glossina palpalis detected in the districts of Bobo-Dioulassou, High Volta, and Gueckedou, French Guinea. The diagnosis was made by the microscopic detection of trypanosomes in lymph glands (fresh preparation), and/or blood (fresh and stained preparations, triple centrifugation), and by the examination of the CSF, counting the cells in a Fuchs-Rosenthal chamber, determining the protein content.by the Siccard-Cantaloube method, and testing the centrifugate of 10 ml. of CSF for trypanosomes.

Mel B was used in 5-percent solution in propylene glycol. The principle of the treatment was based on daily intravenous injections, given in one sequence, or in 2 series separated by a rest period. The total number of injections ranged from 3 to 14, the total duration of the treatment, including rest periods, from 3 to 38 days. The single dose ranged from 2.0 to 4.0 milligrams per kg. of body weight. The progress of the patients was determined by examinations of gland juice, blood, and CSF at various intervals up to 222 days after the end of the treatment. Microscopic blood and gland examinations were performed at least 7 times after end of the treatment.

In 12 patients with trypanosomes in the blood before treatment, the trypanosomes were not to be found by the triple centrifugation method 24 hours after a single intravenous dose varying from 1.5 to 4.0 milligrams per kg. of body weight. In all 50 patients trypanosomes which were present in the cervical lymph glands before treatment were not to be found 24 hours after a single intravenous dose of from 1.5 to 4.0 milligrams per kg. of body weight. In 8 patients, presenting before treatment trypanosomes in the CSF, the parasites were not to be found 7 days after a treatment consisting of 4 intravenous injections of 3.6 milligrams per kg. of body weight each, given at the rate of one a day for 4 consecutive days. In one patient who received only 3 days of treatment with 3 injections, of 3.6 mgs. per kg. of body weight each, the trypanosomes had disappeared from the CSF 7 days after the treatment.

As few as 3 injections applied in 3 days, may reduce cell count and albumin content to normal within two weeks following the end of the treatment; but in the majority of patients the general rule that the cell count approaches normal more rapidly than the albumin content, applies. In patients in whom the cell count has returned to normal, the albumin content may continue to remain high for a long time, or drop more or less slowly.

The 50 cases have been classified in three groups: in 20 cases, forming group I, the cell and albumin content had returned to normal at the end of the last control examination, the control period averaging 108 days; in group II, 23 cases are summarized in which the cell count, but not the albumin content, had returned to normal after a control period averaging 78 days; group III

contains 7 cases, in which both cell count and albumin content were above normal after a control time averaging 70 days, the cell count being significantly reduced and the albumin content stationary or somewhat reduced.

The classification of the cases in the three groups is only temporary. The groups represent stages of recovery through which the patients pass as a function of the time elapsed after the end of the treatment. Obviously, the time required to reach a certain stage of recovery depends to a large extent on individual, uncontrollable factors. As to be expected, the patients showing the least improvement are to be found in group III, corresponding to the shortest average follow-up time, although the patients returned to normal by all criteria are summed up in group I, corresponding to the maximum average follow-up time. The fact may be emphasized that in none of the 50 patients did control examinations reveal the presence of trypanosomes in the CSF, including 20 patients presenting trypanosomes in the CSF before treatment. Coinciding with the CSF controls, blood and lymph glands were examined, with persistently negative results. It may be stated that after the first injection, no trypanosomes were ever encountered in any body fluid examined. Clinical ameloriation set in coincidentally with the disappearance of the trypsnosomes from all body fluids, and progressed essentially on a parallel with the decrease of the cell count, but largely independently of the albumin content of the CSF. Comatous stretcher patients usually started to rise and walk without help one week after the first injection.

Further studies will have to bring out the significance of the increased albumin content of the CSF persisting in a number of patients at the end of the observation period. High total protein content, in the absence of other abnormal findings, may signify nothing but a clinically meaningless residual scar-effect or a precourser of a relapse. Thousands of patients all over Africa continue to be treated with large amounts of arsenicals as a precautionary measure, although they are clinically cured and present no other pathological change than a high albumin content. It is suggested that a qualitative analysis of the CSF albumin may help to select the patients for whom further treatment is really required.

Within the dose limits indicated the treatment with Mel B had no untoward effects. Symptoms of intolerance included albuminuria, gastro-intestinal disturbances, skin manifestations, nervous, and in particular, visual disorders. In 15 cases chosen at random, the white blood cells were checked and found to be unaffected.

On the basis of the experience gained to date, the following routine is suggested for the mass treatment of sleeping sickness in all stages: two series of 4 intravenous doses of 3.6 milligrams per kg. each, applied one dose a day for 4 consecutive days, the two series being separated by a rest period of one week. The scheme should not be applied indiscriminately to patients with extreme symptoms of meningo-encephalitis, such as semi-coma and coma. In such cases

the dosage indicated may be retained, but an interval of several days should be allowed between the first 3 or 4 injections, in order to avoid possible severe Herxheimer type reactions due to sudden massive destruction of parasites in the nervous centers. The question remains open whether it is necessary to apply the second series of 4 injections in first-stage cases. Preliminary data point in this direction, but until definite results are available the full course of 8 injections is recommended. (Am. J. Trop. Med., March '49, E. A. H. Friedheim)

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Appearance of Antibodies to Brain in Human Beings who Receive Anti-Rabies Vaccine: Recent studies have shown that a disseminated type of encephalomyelitis can be produced in experimental animals by the injection of homologous and heterologous brain tissue, and that the lesions produced resemble the lesions found in the demyelinating diseases of human beings including the encephalomyelitis following anti-rabies vaccination. This has suggested the possibility that isoimmunization to brain tissue may be the mechanism responsible for the production of these diseases and, in particular, of the encephalomyelitis following anti-rabies vaccination, because in the latter, the injection of heterologous brain tissue duplicates in many ways the actual experimental procedure which has been followed in animals.

It seemed of interest, therefore, to determine, in a preliminary study whether or not patients receiving anti-rabies vaccine actually develop anti-brain antibodies in their sera. The procedure followed consisted of (1) the immunization of rabbits to determine the antigenicity of the brain extract used, and (2) the titration of the sera of patients receiving the anti-rabies vaccine, with this particular antigen.

The present work confirms that of Lewis in showing that antibodies to brain tissue are produced in the rabbit by the intravenous injection of foreign brain substance. It also provides evidence that antibodies to human brain are produced in patients receiving the Semple anti-rabies vaccine. One case suggests the possibility that a markedly increased antibrain antibody titer may occur in those patients developing an encephalitis following this treatment. (Proc. Soc. Exper. Biol. and Med., April '49, R. C. Kirk and E. E. Ecker)

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Training Course for Naval Reserve Dental Officers: A course of instruction for Reserve dental officers has been established at the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland, during the period from 20 June to 1 July 1949, inclusive. The Naval Dental School has been selected as the facility best equipped and staffed to conduct this training which will consist of lectures, demonstrations and conferences on professional and military subjects appropriate to dental officers of junior rank. Preference will be given, therefore, to applicants in the ranks of lieutenant (jg) and lieutenant.

Because of the lack of space, it has been necessary to limit the attendance to this course to Reserve dental officers east of the Mississippi River. However, it is planned to repeat this training three times each year, and it is hoped that funds will later be available to permit the assignment of officers from all parts of the United States.

The Commandants of the 1st, 3rd, 4th, 5th, 6th, 8th, 9th Naval Districts and the Potomac River Naval Command, and the Chief of Naval Air Reserve Training are authorized to order Reserve dental officers to this course in a training duty status in accordance with the following quotas:

Naval District	Maximum Quota	
1	5	
3	8	
4	5	
5	3	
6	4	
8	4	
9	11	
PRNC	2	
CNARESTRA	2	(east of Mississippi River only)

Officers desiring to attend this course should apply to the commandant of the naval district concerned or the Chief of Naval Air Reserve Training, as the case may be. Sleeping quarters at the Naval Medical Center will be offered to those who may desire such facilities. (Dental Div., BuMed)

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Training and Experience in Leprosy Available: A Navy medical officer is now serving as Officer-in-Charge of the Provisional Leper Colony of the Trust Territories of the Pacific on Tinian, M. I. This officer will be eligible for rotation to duty in the continental United States in March 1950, and the Bureau is now giving thought to the selection of a suitable replacement. It is planned to assign the medical officer selected as replacement to a brief period of indoctrination at the Carville Leprosarium in Louisiana and thereafter to a period of training of from 3 to 4 months under Doctor Sloan at the Leper Colony in Molakai, T. H.

The Bureau of Medicine and Surgery would be pleased to consider applications for this training and duty from medical officers (including those on inactive duty) desirous of furthering their training and experience in the general

field of tropical medicine and in the study and care of leprous patients, in particular.

Government quarters are furnished. The duration of duty in this area is approximately 18 months.

Applications may be made by letter or dispatch and should reach BuMed by 1 July. No service agreement is required. (Personnel Div., BuMed)

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Navy Seeks Civilian Dentists for Trust Territory: Civilian dentists (which includes inactive Reserves in a civilian capacity) are being sought for one year civil service contracts to treat natives of the islands of the Trust Territory in the Pacific Area.

Applicants for the positions, which pay $6,127.50 a year, must pass a physical examination equivalent to that for the Armed Forces, and must agree not to enter civilian practice in the area after their contracts expire.

Interested dentists may obtain applications (U. S. Civil Service Form 57) at any first or second class Post Office. Completed forms, plus references and proof of graduation from a recognized dental school, may be sent to the District Dental Officer, Twelfth Naval District, 50 Fell Street, San Francisco, California.

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Op24B/cj, ND14/A3-1, Serial: 135P24 21 April 1949

To: All Ships and Stations

Subj: U. S. Naval Medical Activities; Change in

1. The following activity is established under a medical officer in charge effective 15 April 1949:

U. S. Naval Medical Unit
Tripler General Hospital
Oahu, T. H. 4206-500
(Mail Address)
Army Post Office No. 438
San Francisco, California

This activity is under the military command and coordination control of the Commandant, Fourteenth Naval District and under the management control of the Bureau of Medicine and Surgery.

2. The Chief of the Bureau of Medicine and Surgery will formulate the mis sion for the subject activity with notification to the Chief of Naval Operations (OP-001D).

3. Bureaus and offices concerned take necessary action.

--SecNav. J. L. Sullivan

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Op24B/cj, NH13/A3-1, Serial: 159P24 22 April 1949

To: All Ships and Stations

Subj: U. S. Naval Hospital Corps School, Naval Hospital, Naval Training Center, Great Lakes, Illinois; Military Command of.

Refs: (a) SecNav ltr Op24/glb Ser 285P24 dated 8 May 1947.
(b) Catalog of Naval Activities, 1 January 1949.

1. The U. S. Naval Hospital Corps School, Great Lakes, Illinois (Code 7439-366), is hereby removed from the military command of the U. S. Naval Training Center, Great Lakes, Illinois, and placed under the military command of the U. S. Naval Hospital, Great Lakes, Illinois.

2. References (a) and (b) are modified accordingly.

--SecNav. J. L. Sullivan

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BUMED CIRCULAR LETTER 49-60 11 May 1949

To: All Navy and Marine Corps Separation Activities

Subj: Separation from the Naval Service of Personnel having a Venereal Disease; Procedure for

Refs: (a) BuPers C/L 6-49 dtd 13 Jan 1949.
(b) Par. 12B6, 3329, 16A8, and 339.2, MMD.

1. The general policies expressed in Ref (b) are interpreted in the case of venereal disease to mean that no person with venereal disease in a communicable state shall be released from the naval service until the individual has been rendered noninfectious and not a menace to the public health. The following policies shall be strictly adhered to:

(a) A presumptive and/or standard serologic test for syphilis shall be made on all persons about to be discharged or released from active duty. This test must be made within seven days of the expiration of enlistment or date of discharge and the results recorded in the Medical History Sheet.

(b) Personnel, who on physical examination have signs, symptoms or findings of a venereal disease in an infectious state, should be retained in service and transferred to a naval hospital for further diagnostic study and treatment, if necessary.

(c) All Health Records shall be thoroughly checked and those containing an entry indicating that the individual has or has had a venereal disease, or that the blood test made just prior to separation is reported as positive or doubtful, shall be reviewed by a medical officer and the individual grouped in one of the following categories and handled accordingly:

CATEGORY A: Includes all personnel who have a history of venereal infection with adequate follow-up examinations, including spinal fluid examinations and blood determination in syphilis cases.

NOTE: (1) Syphilis cases should have spinal fluid examination six months post treatment.

(2) Blood tests should also be performed on gonorrhea cases at least six months after treatment in order to determine if this disease masked an undetected case of syphilis.

Procedure: These individuals shall be personally interviewed and given both verbal and printed advice (NavMed-911) relative to their status and previous treatment. The Separation Epidemiologic Report is not required in these cases.

CATEGORY B: Includes all personnel who have a history of venereal infection within a time period, and personnel with a clinical course or with incomplete treatment who require further follow-up examinations or treatment before reasonable assurance of cure can be given. (Includes syphilis treated within one year of separation and gonorrhea treated with penicillin within six months of separation.)

Procedure: (a) These individuals shall be personally interviewed and given both verbal and printed advice (NavMed-912) relative to their status and previous treatment.

(b) Instruct the individual to report to his private physician, to a Rapid Treatment Center, Veterans Administration Representative, or to a Venereal Disease Clinic near his place of residence for follow-up examinations.

(c) Complete the Separation Epidemiologic Report.

CATEGORY C: Includes all personnel who have a positive or doubtful separation blood test but no history of venereal infection and whose physical examination reveals no clinical signs or symptoms of venereal disease.

Procedure: (a) These individuals shall be personally interviewed and given both verbal and printed advice (NavMed-913) relative to their status. They should be given either the privilege of receiving hospitalization and treatment or separation from the service. They should be informed, however, that if complications develop and they have not received treatment while in service, it is probable they will be declared ineligible for benefits of service-connected disability.

(b) If treatment in the service is elected, transfer to a naval hospital for diagnostic study. If indicated, treatment in the hospital should consist of a standard course of therapy. An individual need not be held for follow-up examinations but should be instructed to consult his private physician or report to a Rapid Treatment Center, Veterans Administration Representative, or Venereal Disease Clinic near his place of residence. Upon discharge from the hospital, handle as in Category B.

(c) If treatment in the service is not elected, an individual should be referred to his private physician, to a Rapid Treatment Center, Veterans Administration Representative, or to a Venereal Disease Clinic for treatment and follow-up examinations.

(d) Complete the Separation Epidemiologic Report. A notation of any pertinent information (recent malaria, smallpox vaccination, infectious mononucleosis, etc.) contained in the Health

Record that might explain the serological reaction should be placed under "Remarks" on this form.

2. The Separation Epidemiologic Report shall be completed in quadruplicate on individuals falling within Categories B and C and shall be forwarded as follows: Original copy to Buined; second copy to the Veterans Administration, Dermatology and Syphilology Section, Room 5008, Munitions Bldg., Washington 25, D. C.; third copy to the State Health Department of the state to which the individual goes after separation; and fourth copy to the individual. NavMed-911, 912, and 913 as appropriate, shall be given to individuals in each of the above categories. These forms should be carefully explained to the patient and should be read over with the patient to insure that he understands the contents.

3. Excepted from the provisions of paragraph 1, subparagraphs (b) and (c) are all persons who are to be immediately re-enlisted and have a positive or doubtful serologic test. Such persons may be re-enlisted and transferred to a naval hospital for further study and treatment, if necessary.

4. When referring patients to civilian health agencies, reference should be made to the latest Directory of Venereal Disease Clinics as published by the U. S. Public Health Service.

5. Consultation and assistance in implementing the above procedures will be available from District Venereal Disease Control Officers upon request to the District Medical Officer or River Command Senior Medical Officer.

6. Separation Epidemiologic Reports (FSA USPHS Form PHS-691(VD) Rev. 2-48) (old No. 9576B), Forms NavMed-911, 912, 913, and the Directory of Venereal Disease Clinics, may be obtained by request to the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

7. These instructions will be incorporated in future changes in the Manual of the Medical Department.

--BuMed. C. J. Brown

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BUMED CIRCULAR LETTER 49-61 23 May 1949

To: All Holders of Manual of Medical Department

Subj: Certificate of Death NavMed-N (Revised 1-1-49)

Ref: Manual of the Medical Department, Pt III, Ch 4.

This letter (1) states that the Certificate of Death (NAVMED-N) has been revised (see News Letter of 6 May 1949, page 31) and revised forms are now in process of distribution, that upon receipt of the revised forms and this directive the new forms shall be put into use and all old NAVMED-Ns on hand shall be destroyed, that appropriate changes in reference (a) will be made in a forthcoming revision, and (2) contains detailed instructions and interpretations that are to be followed regarding certain specific items.

NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

OFFICIAL BUSINESS

Permit No. 1048
NavMed-369 - 6/49-27,900

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